California Institute for Regenerative Medicine
Scientific Meeting for ICOC and Public
California Institute of Technology
May 25, 2006 (9:00am-3:00pm PDT)

Zach Hall, PhD; President, California Institute for Regenerative Medicine
Welcome and Introduction

- Zach began the meeting with an introduction of the CIRM staff and ICOC Board members who were in attendance.

- He continued to say that we are engaged in a process that will take roughly six months and it is extremely important as it will lay out the blueprint for how CIRM spends its money over the next 10 years.
  - The first phase is an information collecting phase and we are conducting a series of interviews and expect that we'll do 60-75 interviews before the process is over.

- The other part of the plan is to have four meetings that involve the ICOC as it will be finally responsible for adopting the plan.
  - The first two are formal ICOC meetings on June 2 and Aug 2 and we have reserved the evening before for discussion as well.
  - We also have CIRM scientific meeting for the ICOC and the public. The first is May 25th and the second is Jul 13. These are not formal Bagley-Keene meetings but they are public meetings.

- Zach next provided an overview of the process.
  - He described stem cell research as a process extending in time. Since the field will continue decades into the future, in a sense, the Institute's ten year plan is an early and arbitrary point in what will be a long and ongoing process for the field as a whole.
  - CIRM will need to develop its long term objectives in the clinical, translational, basic science, and infrastructure areas.
  - CIRM also hopes that we will have some stem cell based therapies in the clinic but the work in the field will go on well beyond that point. It takes years to develop therapies and therapies for different disorders develop at different rates, so this is only a beginning.
  - The clinical developments that happen after ten years will be based on accomplishments in translational and basic science. This will be an ongoing process and CIRM will need to have active work in each of these areas throughout its tenure.
  - CIRM also hopes to build infrastructure and wants this to endure beyond the ten year timeline.

- The first task will be to ask the ICOC to populate long term objectives in each of the aforementioned areas and to define a mission statement.

- Arriving at these objectives will occur through a series of initiatives CIRM will carry out in these areas. These initiatives will advance work in each area. CIRM also wants initiatives that cut across these areas.
- This will be the core of the plan - how we structure these initiatives.

- One of the first question CIRM will ask is: "What values do we want these initiatives to embody?" and the August ICOC meeting will address this question. A second question is: "What are the scietific and clinical challenges we will face?" This will be a subject of a meeting similar to this meeting that will take place in July 13th.

- Today's meeting will focus on funding structures, that is, on how CIRM can put its initiatives together to maximize progress, get the people it needs, encourage discovery, carry out directed research, bring in technologies from other areas, and provide core services and facilities. Two other key questions are:
  - How do we enhance basic science / clinical interactions?
  - How do we encourage and facilitate interactions between non-profit research institutions, where much of the basic science and some early phase clinical science gets done and the commercial sector where much of the translation work and later stage clinical work goes on?

- Zach concluded by mentioned that while CIRM has a series of questions, it doesn't have to be confined to them, and that the talks to be given today are from people who have something to tell us based on their own experience that may help us answer those questions.

(Note: For the following section, the numbers following each major bullet refer to the number of the slide being discussed)

Michael Rudnicki, MD, PhD; University of Ottawa, Canada
"The Canadian Stem Cell Network"

Presentation

- 1 - I'm going to talk about organization of Canadian Stem Cell Network (CSCN), what our goals are, the grant process, and what we achieve through these initiatives.

- 2 - Drs. Metilla and Hill were awarded prizes for stem cell research and are being considered for the Nobel Prize. These individuals left a legacy that formed the foundation for future scientists.

- 3 - This is the regulatory framework for industry and academia for working with stem cells. Canada has a national review board that looks at all experiments

- 4 - We have formed a Network of Centers of Excellence that bridges the gap between industry and academia. It was created to benefit the economy and quality of life of Canadians. Program criteria encompasses the following:
  - Excellence of research
  - Training / Development of Personnel
  - Network and partnerships
  - Knowledge and technology exchange exploitation
  - Management of the network

- 5 - The Stem Cell Network was founded in 2001. It was given $37M over 7 years by the Network of Centers of Excellence and this amount can be renewed after 7 years. We have doubled this funding through partnerships. We currently have 74 scientists in the network.

- 6 - The Stem Cell Network is incorporated and has a Board of Directors. A number of leaders from different areas make up the management team. Bioengineers, lawyers, clinicians, scientists, and ethicists are all part of the management team.

- 7 - The mission of the SCN is to function as catalyst for realizing full potential of stem cell research for Canadians.

- 8 - Our approach is to implement research programs that would allow us to identify and pursue key problems that will help entire field. We don't pursue individual diseases. We try to push promising products through the pipeline and conduct research under an ethical framework.

- 9 - We have a research management committee with the team leaders, management from within and outside of the network, and representatives from industry.
  - We are not discovery research driven. We are goal directed and translational with the goal of pushing things towards the clinic.
  - Project managers support each project to facilitate project performance against milestones and budget
  - Projects which are not meeting milestones and not promising can be downscaled and projects that are doing well can be scaled up. Programs are not seen as static and work can move from lab to lab depending how it is proceeding.

- 10 - The Network originally pursued 6 disease areas but this was problematic to limit things to disease areas. Rather than pursue diseases, the network is pursuing 4 strategic programs
  - Stem Cell Applications & Cellular Therapy
  - Stem Cell Therapeutics & Drug Discovery
  - Tools, Reagents & Diagnostics
  - Stem Cells & Public Policy

- 11 - This slide shows our strategic workshop map. Originally, we had a disease focused structure, but we moved away from a disease focused approached and toward pursuing enabling technologies potentially applicable to many disease areas.

- 12 - This slide shows our strategic program overview that was the result of redirecting our efforts into pursuing enabling technologies.
- We utilize two funding strategies, “catalyst” grants which are small 1 year awards and “core” program awards.

- 13 to 15 - This is our core project review process. Steps involved were derivation, growth, and directed differentiation. Projects require ongoing reiterative discussion which allows projects to be redefined in real time. We do not "grant and forget".
  - Through a hands-on procedure, we were able to meld and mold our efforts into the direction we wanted to pursue.

- 16 - Our International Scientific Review panel performed the review process.
  - These programs were reviewed by an independent scientific advisory board; we did not want to be seen as "old boys' network".

- 17 - The review criteria were as follows:
  - Relevance to a SCN strategic program
  - Research excellence
  - Project management
  - Networking & partnerships
  - Knowledge exchange & technology transfer
  - Highly qualified personnel

- 18 to 20 - This is our Core Project Review Process

- 21 - We now have 12 core research projects and these are the leaders of the multi-investigator teams.

- 22 - Projects are disease based but they are focused on technologies that are broad and applicable. As we move forward we will look to expand on developmental work.

- 23 - This is our overall research portfolio. Core projects are guaranteed funding for 2.5 years and can be renewed. The bottom number represents partner investment and is important for the leveraging that goes on. We want projects to grow and we have Catalyst grants to assist with this; catalyst grants are small 1 year grant funded 50:50 by the Network and a partner.

- 24 - This is our current funding among different areas.

- 25 - We have a multi-level commercialization policy; the founding of Aggregate Therapeutics is our greatest achievement. CSCN promotes commercialization through:
  - Research emphasizing programs
    - Clinically / commercially relevant research
    - Collaborative projects to stimulate and share IP
  - Develop enabling programs
    - IP protection
    - IP Toolkit

- Enhanced capacity to exploit IP
  - Commercial partnerships
  - Aggregate Therapeutics

- 26 - We also have an IP Tool Kit that helps us figure out how to capture IP from multiple institutions.
  - Jim Price spent 2 years going from institution to institution establishing an IP best practices toolkit.
  - Originally, the 6 largest institutions in Canada signed and then others also signed on.

- 27 - Aggregate Therapeutics is owned by 16 leading Canadian institutions and hospitals and 37 leading stem cell researchers.
  - It has the right of first refusal for technology and can act as IP integrator across institutions.
  - It as a strong management team with biotech and pharma experience.

Discussion

Q (Don Reed): What about government regulations? Is there any chances Canada will do SCNT?
A: Many projects have ELSI components whereas others do not.
- We're looking at issues around cord blood banking in a private system.
- We're also looking at the international landscape on how different institutions regulate stem cell research and how it would affect stem cell research.
- Under current legislation we can't do nuclear transfer. Current legislation can be reviewed every 3 years.

Q (Michael Barrow, City of Hope): How do you go about brokering deals, that is, structuring the grants?
A: Some projects were very directed and we provided feedback and direction to make the strongest project. Others were not as directed. It is an iterative process after we receive letters of intent.

Q (Arlene Chiu): Who provides input into this process?
A: The research management committee. The Strategic Advisory Board says what is scientifically excellent but may not know about the management aspect.

Michael Amos, PhD; Advanced Technology Program,
National Institute of Standards and Technology
"The Advanced Technology Program; Innovative Technology Solutions Through Industry-led Public Private Partnerships"

Presentation

- 1 - Arlene Chiu and I worked together when she was at NIH. We had many interesting discussions together on the topic of funding.

- 2 - Board was conceived under the Reagan administration.
  - The goal was to address the nation's need to come out with new and innovative technologies.
  - The mission is to accelerate the developments of innovative technologies for broad national benefits through partnerships with the private sector.
  - NIST has had 3 Nobel prizes in the last 4 years.

- 3 - ATP has been in existence for 16 years. It is a well kept secret. ATP laid groundwork for a lot of this.

- 4 - ATP uses a funding mechanism through open or general competitions and through focused programs where industry leaders get together with government folks and make statements of needs for certain technologies.
  - Our most well known funded projects are DNA diagnostics and the human genome.
  - ACLARA, Affymetrix, and 3rd Wave all got started and or grew with ATP funding.
  - Many times, ATP is the last hope to get funding. It was created to convince industry to take on more risk than they normally would. It has a peer review system that maintains the proprietary aspects of technologies. It involves stringent confidentiality agreements - and can't use things that are made in proposal.
  - It has strict and careful controls for managing proposals. In 16 years to our knowledge, no proprietary information has been leaked.
  - ATP also has the ability to evaluate multidisciplinary proposals.

- 5 - How do we decide what proposals to fund?
  - 50% Scientific and technological merit
  - 50% Potential for broad based economic benefits

- 6 to 7 - The selection criteria break down as follows:
  - 50% scientific and technological merit
    - Technical rationale, including technological innovation and the level of technical risk and feasibility
    - R&D plan
  - 50% Potential for Broad Based Economic benefits
    - Economic benefits
    - Need for ATP funding

- Pathway to economic benefit

- 7 - We have a panel of savvy business reviewers who understand what it takes to commercialize a product. VC runs a 10% success rate to commercialization; we hit about 60%.
  - About 12% of proposals that come into ATP are fundable and meet all 6 the criteria. If they don't meet one of the criteria they don't get funded; they have to meet all six.

- 8 - For single companies they cover overhead and we cover research up to a $2M cap. For joint ventures it is different.
  - For example, Affymetrix is our largest joint venture to date at about $63M. We put in half and they put in half.

- 9 - We usually get 5 or 6 proposals that are out of this world. We also get just nutty proposals. Some stuff we get is so amazing but just doesn't fit. Our four gates are as a follows:

  - Gate1 - Submission of full technical plan and preliminary economic / business plan
  - Gate 2 - Submission of full economic business proposal and budget info
  - Gate 3 - Semifinalists identified
  - Gate 4 - Award made

- 10 - Gate 1 is a complete technical plan. Every failed proposal gets a personal debriefing. ATP staff will explain exactly why a project proposal failed and was not funded.

- 11 - Innovation at ATP is a unique approach to developing science. It can be a new approach or a novel integration of existing technology. We look for a high probability of failure.

- 12 - We want to revolutionize the state of the art. The resulting technology should be platform technology like Affymetrix. We are not looking for incremental / evolutionary science.

- 13 - We also need to weigh high technical risk and feasibility.

- 14 - We also look at how respondents' plans will be managed and how they will reach their goals?
  - We need to look at people, milestones, and metrics.
  - We have to ask if the people who wrote the proposal have the necessary management skills.

- 15 - Gate 2 is a complete economic / business plan.
  - They need to fully address the potential for economic benefits.
  - It must have commercial potential. If it doesn't, then the Department of Commerce doesn't want to fund it.

- 16 - Both the ATP perspective and Industry perspective must be considered

- ATP cares about net benefits for the nation
- Private investors care about near-term return on their investment.

- 17 - The project must push the envelope and be too risky for private funds

- 18 - The plan must feature a pathway to U.S. economic growth.

- 19 - Gate 3 is selection of the semifinalists. Semifinalists are invited to NIST for an oral review and may be asked to provide written responses.

Discussion

- **Q (Unidentified Audience Member, UCLA):** Who controls the IP? What benefits does the government get?
  - **A:** This initiative is industry driven. The company controls the IP. Companies receive all the benefit. The benefit coming back to government is in a positive effect to the economy and taxes. Affymetrix is a $5B company and the 40% tax rate covers the investment.

- **Q (Jean Fontana, Burnham Institute):** When coming up with policies where states can benefit through IP, how should they form partnerships with industry?
  - **A:** The issue is fairness - if we formed partnerships with companies we have to form partnerships with everyone otherwise they would call their congressmen and complain and this is something we don't want.
    - The main point of ATP is how you encourage companies to take on more risk when they have good ideas.
    - ATP does not approach any entity - it is driven by companies.
    - If you want to force change you have to push the envelope. The only rule is companies must maintain IP in the US; they cannot sell it to a foreign based company.

- **Q (Unidentified Audience Member):** CIRM could theoretically limit IP to California-based companies - you may want to consider this for California.

Presentation, cont.

- 20 - Gate 4 is the award stage

- 21 - We have a number of adult stem cell research projects.
  - We've been funding these projects since 1997.
  - Our most famous is Osiris. They have two products funded from ATP that are now in the clinic. The clinical trials are ongoing - they have completed enrollment for those studies. Osiris would credit us for saving them in rough times.
  - Another famous group we funded is the ACT group in Massachusetts that does transdifferentiation research.

- 22 - The first stem cell project funded was 1992 and we have funded a number of companies in this area.

- 23 - We have a project management team of 3 (a technical specialist, a business specialist, and a grants specialist). We only require one person to read the proposal but request backup.
  - We ask grant recipients for quarterly business reports. There is great accountability in the project management process. We ask for technical and financial reports.
  - ATP does not fund basic research or pure product development. We fund technology development.

- 24 - Our project management objectives focus on starting with high risk projects but moving down as you overcome obstacles. At end of project you should have some sort of prototype.

- 25 - We try to address avoidable issues. There are unavoidable issues that always surface:
  - Key personnel leave
  - Subcontractor issues arise
  - Bankruptcy occurs
  - The company is sold to foreign entity.

- 26 - In 16 years of existence we have disbursed $44B to 768 companies.

- 27 - 34% of our funds distributed to date have gone to large companies and 66% to small companies.

Discussion, cont.

- **Q (Fontana):** Do you have trouble with the lack of transparency during the review process?
  - **A:** The process is audited by the Office of Management and Budget and there is a competition manager who overseas the whole process, so the process is well managed.
    - From the outside world perspective, if you are going to get companies to share their coolest ideas, they will not share unless confidentiality can be ensured.

- **Q (Unidentified Audience Member):** Do you envision CIRM having this role?
  - **A (Zach Hall):** That is one of the options we are here to discuss,

Richard Insel, M.D.; Executive VP of Research, Juvenile Diabetes Research Foundation
"Research Strategy and Funding Programs of the Juvenile Diabetes Research Foundation"

Presentation

- 1 - Title Slide

- 2 - We will spend time talking about our strategy and implementation approaches. Our mission is constant - to find a cure for type I diabetes and its complications. We look to develop new approaches to accelerate to this mission.
  - FY 2006 had research funding of $120M. 35% of funding goes outside the U.S.
  - In FY 2005 we had 500+ investigators in 19 countries.
  - It is important for foundation to address issues of reimbursement policies. Whatever we develop we want to be affordable regardless of the patients' socioeconomic status.

- 3 - We review grants not only on the basis of science, but also the fit for our portfolio and the pressing needs to move the research forward. Our goal is to find "cure therapeutics."

- 4 - One of our goals is to restore Beta cell function and our interests in stem cells lie in finding a way to restore beta cells.

- 5 - Historically, JDRF has been a funding agency and we are moving beyond that and becoming an operating agency. Looking beyond that, we want to be an R&D agency, a virtual therapeutics R&D company

- 6 - This slide illustrates the ideal and optimum cycle to discover, develop, and deliver Type 1 diabetes therapeutics.
  - The academic sector does well in the arena of discovery. Historically JDRF funded only discovery, now its purview has broadened. How do we move from discovery to looking at drug targets, drug candidates, etc?
  - We distinguish clinical research from clinical development.
    - Clinical research ideally gets you to proof of concept. Clinical development moves you towards market approval.
    - From the time a drug candidate is identified to the time it makes it to market is about 10 years with a cost of $1-1.8 billion (including failures). We also are faced with regulatory issues and we have to be smart.
    - Portfolio, proactive management, and partners, these are our 3 Ps. At each of the steps in the cycle, we need to partner with a different group. We have to ask "How do we best get to the end game?" which is the patient.

- 7 - We're starting to push the translation envelope for projects to obtain Proof of Concept and to develop a commercially viable product.

- 8 - The JDRF strategy is:
  - To take risks; we will do the studies to 'de-risk' a project in order to attract a partner who will develop the drug.
  - To champion.
  - To accelerate our mission and "mind the gaps" - scientific, funding, and regulatory. We feel we can bring the most value by bridging the gaps.

- 9 - We aim for the creation of a balanced portfolio. Clinical development is commercially driven to obtain market approval.
  - The portfolio driven across the basic, translational, and clinical spectrum.

- 10 - Our research grants are as follows
  - Our regular research grant is $165,000 for 3 years.
  - Our Innovative Grants are for $110,000 for 1 year, and we saw an increase in proposals of 80% after we doubled the funding to get to this level.
    - Proposals accepted 3 times per year with a response in 3 months; applications have gone up 60% with this approach
    - We have tracked our innovative grants and they have been successful at leading to NIH or further JDRF funding as well as to publications in top notch peer reviewed journals.
  - The JDRF Scholar Award is modeled after NIH Pioneer award. Here we are betting on the jockey. The focus is on high risk / highly innovative research. Recipients can get up to $250,000 per year for 5 years. Will award 3-4 this year and 3-4 for the next few years to reach a steady state of ~ 14 active awards at any one time.
  - Our Program Project Grants offer up to $660,000/year for 3 years
  - Our "Innovative Partnerships" brings together innovative scientists with people from different backgrounds. We try to bring together biologists / clinicians / etc.

- 11 - In fiscal year 2005, we spent 8% of our financial resources in training through Career Development Awards, Early Career Research Awards, Postdoctoral Fellowships, and Advanced Postdoctoral Fellowships. All details of awards are on our website.

- 12 - We also have JDRF Translational Research Grants
  - JDRF Centers in Immunology/Prevention; Islet Transplantation; and Complications. These awards are up to $2Million/year for 5 years
  - Clinical Investigations Research Grants offer up to $660,000/year for 5 years and supports both clinical research (non-intervention) and clinical trials.

- 13 - We have a number of international partners. We normally put up matching funds. We have stem cell partnerships in 7 different countries; 10% of our funding goes towards stem cells.

- 14 - We have partnerships in stem cell research to create pathways to move from discovery to proof of concept and into the clinic.
  - This allows us to leverage our resources more effectively by taking advantage of existing infrastructure.

- 15 - We have partnerships with the National Institutes of Health, Centers for Disease Control and Prevention, the Department of Defense, and NASA

- 16 - This slide illustrates the structure of one of our partnerships

- 17 – We have set up JDRF and actively managed our efforts and in many cases actively designed programs where we believe focus in certain areas is required to deliver therapeutics. Such programs include the following :
  - Strategic Projects
  - Invited R&D Grants
  - Team Science
  - Industry Partnerships

- 18 - Our strategic projects evaluation criteria look at things from a research and development and business standpoint. It is difficult to know about commercial viability early on.

- 19 – Successful clinical proof of concept takes a lot of risk out of project development. Some of our strategic projects are very early stage. Examples are biomarkers of efficacy and safety, and access to patients for clinical trials.
  - We also look at a defined regulatory pathway and reimbursement policy. We have hired consultants to work with us in developing regulatory and reimbursement strategies with the appropriate agencies for our artificial pancreatic project.

- 20 - JDRF's team science approach is such that if you make progress you get more money and if you hit a bottleneck you may get more money to help you push through it.
  - A lot of good things happen when you bring people from multiple disciplines together.
  - This function is facilitated by a strategic program director who may not necessarily be scientifically expert in specific project area.

- 21 - We had to set up sub-teams in "Regeneration of Beta Cell Function" project, one of our "team science" actively managed programs. We just got too big too fast.
  - We have monthly oral reports and quarterly written reports
  - We have unique resources and this group has access to unique libraries and instruments.
  - These are the kinds of tools that investigators at Academic Medical Centers AMCs don't always have access to. It provides a new dimension to their labs.

- 22 and 23 - Our Industry program (Industry Discovery and Development Partnerships) is new. Partnerships are typically for 1-2 years. Companies are expected to match and many do more than match. We are not a venture capital group, so we don't see it as investing, but see it as a partnership.
  - Milestones often change; it is a very dynamic effort. We try to visit companies at least 1 a year to "kick the tires". Payments are made quarterly based on progress
  - Proposals undergo scientific, business and lay review. We look at it from the standpoint of commercial and technical viability. Venture capitalists assess commercial viability.
  - We require a quarterly written report. A separate research development program of lay volunteers oversees the activities of this program.

- 24 - JDRF views its role as facilitating and fostering research and "community building."

- 27 - We fund the webpage for ISSCR

Discussion

- **Q (Unidentified Audience Member, UCLA):** Are you pleased with the results of funding? What advice would you give us? What mistakes have you made that we can learn from?
  - A: Our mission is to cure disease. We want to get therapies to clinic. That is our report card - not publications.
    - We do understand you need a good foundation of science in order to get them. We have acquired a lot of knowledge.
    - We have fallen down in how to translate. We need to improve in moving from the discovery - development stage into the clinic and moving across the spectrum.
    - How can we complement universities? Do we need to partner with biotech and pharma to develop drugs? There is no drug that was developed by academia and commercialized well. Pharma and biotech does it well.

- **Q (John Simpson, Foundation for Taxpayer and Consumer Rights):** How have (WARF) patents affected ESC research funding decisions?
  - A: We are funding both in and out of the US. I can't quantify how much it has impeded us financially. I will say we are concerned with WARF policy.
  - Patients are a priority and we need to be aware of urgency as we move forward. If we fund purely exploratory research, we will never get there. We need to get there and push therapies to clinic.

Ethan Singer, PhD; High Q Foundation
"Managing the Search for Huntington Disease Therapy"

Presentation

- 1 - Introduction Slide. All speakers today have described non-traditional funding mechanisms.

- 2 - We are working with changing therapeutic paradigms and raised expectations.

- 3 - We are a not for profit foundation and have been in operation 4.5 years. High Q currently funds over 150 projects both academic and industrial. The 2005 budget is $25M.
  - We have no Scientific Advisory Board but rather have expert advisory groups and convene workshops on areas we are interested in (biomarkers, mouse testing, etc).
  - We try to leverage and leverage the cutting edge of academic research to pursue drugs.

- 4 - High Q directly supports research that identifies and validates targets for drugs as well as biomarker development. High Q's drug discovery and development is conducted through CHDI Inc, a non-profit drug discovery and development company. We are a virtual company and have no wet labs. High Q and CHDI do preclinical testing. HD Therapeutics does clinical trials. This is how we move across the bench to bedside continuum.
  - Clinical trials are primarily run by HSG for US trials and by EHDN (based in Germany) for international ones.

- 5 - High Q is a large and growing organization devoted to mission

- 6 - Huntington Disease is a genetic disorder and everyone who has the gene will eventually develop the disease.
  - It affects roughly 30,000 in US.
  - The disease can manifest at any age. People who manifest the disease range across the spectrum, but you get the disease typically at middle age.

- 7 - High Q has an integrated program and we want to support everything we can. We don't want to be in position of saying: "if only we had supported it 2-3 years ago".
  - We have very good private funding which makes a big difference. We are fortunate to not have large concerns about fundraising.

- 8 - The CHDI, Inc pipeline has candidates in screening but no drugs in it yet.

- 9 - The use of stem cells for Huntington's disease involves repopulation of lost brain cells by stem cell transplantation.
  - We do close monitoring of the transplantation field, but it is far down the road for us so we are not supporting anything in this field.
  - There are stem cells in the brain, so repopulation of lost brain cells by endogenous stem cell mobilization may be promising.
  - We are discussing potential projects in this area with researchers.
  - In order to develop drugs we would like to test potential drugs in vitro against cells in culture. The problem is they are highly differentiated cells.
    - We are looking for differentiation of cultured stem cells into brain-like cells for drug screening. We would also like to standardize culture conditions.

- 10 - Comparative Research Capabilities.
  - NIH: Discovery research is broad-based for targets and technologies and drug development is minimal.
  - Industry: Discovery research is minimal and is largely from academics. Drug development is extensive and thorough and proceeds through clinical trials and registration.
  - High Q: We use a broad based approach for targets and technologies and involve academics and CROs. Drug development, like with industry, will be extensive and thorough, and proceed through to clinical trials.

- 11 - Investigators
  - NIH: Done through academics and collaborations.
  - Industry: Done through own employees and strategic alliances
  - High Q: Uses academics, CROs, the HD research community, collaboration, and interaction.

- 12 - Decision on Research Projects to Pursue
  - NIH: Has standing programs, RFPs, research areas, and maximizes use of limited funds.
  - Industry: Relies on executive decision and corporate programs to maximize return on investment
  - High Q: Does not issue RFPs. We decide what needs to be done and then have proactive recruitment, inquiries, and workshops to determine the critical path to therapy and seek out enabling technologies. The goal is to maximize speed.
    - We actively recruit laboratories that may be best suited for the research. We also have a website that people stumble across. We do not do things serially, but in parallel instead.

- 13 - Research Proposals
  - NIH: Requires extensive documentation, uses a study section that makes a fund or don't fund decision, and typically has a 9 month turn around.
  - Industry: The process is internal, is affected by executive decision, and has a rapid turnaround.
  - High Q: Requires a letter of intent (LOI), about 250 words. If HighQ likes the LOI, they then invite a brief proposal. The proposal should cover what you plan to do, how much money you need, and how will it lead to therapy. We have interactive refinement and "shaping" of the proposal with the applicant and typically have a 6-8 week turnaround to a decision.
    - If you can't get to therapy we are not interested in funding it - that is what NIH is for.
    - The proposal is 5 pages long - we want them in the lab, not at the desk. We will provide feedback to investigators to get to a project that supports our goals and the investigator's needs.

- 14 - Research Agreement
  - NIH: Uses grants (often multi-year) and is subject to Bayh-Dole
  - Industry: Uses contracts, is governed by executive decisions, and intellectual property is proprietary.
  - High Q: We use contracts, preferably one-year. We use longer contracts if necessary. All patent applications derived from a contract related to HD are for community use. The IP from non-HD applications is up to the partner's choice.
    - This allows us to monitor the progress of research as it is going on. Any use for HD can be disseminated among the research community.

- 15 - Measuring Research Progress
  - NIH: Has minimal oversight, requires specific aims, and likes to see publications as a measure of output.
  - Industry: Has continual monitoring, required milestones, and deliverables / products.

- High Q: We have midcourse corrections and milestones, though not necessarily products.
  - You have to do the experiment you said you were going to do. The deliverable is to run the experiment.

- 16 - We use a decision tree to develop a target validation score that runs from 0 to 5 in increments of 0.5. We judge the project by whether or not if will be successful in driving something to the clinic.

- 17 - For proposal processing, we recruit, take inquiries, and do workshops. We have an internal and external review and evaluate and discuss with the principal investigator.

- 18 - We have a narrow focus and a tight organizational structure. Our staff is full-time and highly experienced. Our business has a professional management and a sound and sensible IP policy. Our science involves critical path research only.
  - We try blanketing all research areas insofar as possible. Speed is the bottom line.
  - We fund both academic and industrial research.
  - We have milestones and deliverables rather than aims and goals.
  - We have extensive and thorough interaction (shaping), midcourse correction, distribution, and sharing of materials and technologies.

- Conclusion - I can't tell you if our system works until we have a drug but I hope we are on the right track.

Discussion

- **Q (Chiu):** How many projects do you fund?
  - **A:** we funded 150 projects for a total of $25M FY06

- **Q (Unidentified Audience Member, UCLA):** How important is your relationship with industry? How have you been teaching constituents patience with regards to scientific process?
  - **A:** My personal answer is to be as transparent as possible. Patients deserve to know exactly what is going on.
    - As research progresses, we are finding more measurable features before HD onset.
    - Is it useful to have the term onset? I personally favor that you have to tell people they have disease even without motor signs.
    - As science goes on, results presented in literature don't hold up.

- **Q (Richard Insel):** How do you manage expectations?
  - **A:** We need more than just home runs. We need singles and doubles that may impact the lives of patients. These may not be cures, but they will impact their lives.
    - We need to be very realistic as we move along and have interim steps you can point to as progress.
    - With all these diseases people are trying to develop cures for we should put money into drug development and into cure development.

- **Comment (Amos)**: You may have to take orphan indications where you may not be able to entice industries to go in. Companies are looking for chronic diseases. It is something you have to think about.
- **Comment (Mary Maxon, CIRM)**: A lot of companies have significant discovery interests internally. They turn to SPRI grants from government. From my experience, there is significant research going on inside companies.

- **Q (Unidentified Audience Member, City of Hope):** To what extent does CIRM view itself as replacing and / or going beyond the federal role in funding research?
  - **A (Hall):** There is no money going into hESC work for non-approved hESC lines.

- **Q (Simpson)**: There is an IP policy being developed for CIRM. Can we see your IP policy and get some insight from it?
  - **A (Hall):** I will give you Dr Insel's contact information.

Jonathan Shestack; Co-founder, Cure Autism Now (CAN)

Presentation

- When CAN was founded (in 1995), there was maybe $5M of federal money going into autism annually but that was debatable because there was no way to really find out how much federal funding there really was.
  - This worked out to about $12 per person for the number of people who we thought had autism, which was also incorrect at the time. We thought it was worse and it was worse.
  - The private community was putting nothing in and there were maybe a dozen scientists who were working on autism and they were not well funded. They were also often clinicians, so they never had time to get controls or write up a study in a way that could be replicated or even published.
  - The previous sense was that there was no reason to do any research - for many years there was a feeling that autism was a psychiatric disorder with psychiatric causes or caused by bad parenting or trauma. But then in 80s, a few researchers, including one at UCLA, decided perhaps it was genetic and started doing work in that area.

- We had a different problem than CIRM has: there was no money and pretty much no interest. It was our job to push this uphill from scratch.
  - We first put together a group of advisors; we couldn't find many autism advisors so we looked outside the field. They looked at what little we had and said it was pretty interesting. While people hadn't been working in autism they had been working in other neurological disorders and thought we could make progress in our field.
  - The first thing our advisors said was we would have to overpay. So we started a pilot grant program and overpaid and started to get the first group of people in. We raised $400K in the first year and couldn't find $400K of good research to fund, but each year it got better and better.

- We learned a lot from friends in other fields like Nancy Wexler and people involved in Huntington's. We did little things to get people together, like, for example, convening a workshop on specific issues like animal models in autism or the GI tract in autism, which was something important anecdotally to the parents. We would invite a lot people from those other fields and the autism field and get them together.
  - We also made an effort to introduce the scientists doing the work to people who have the disease. It's a really good idea. It's amazing - putting a human face on it is always good and made it a more urgent. From those workshops we would issue RFAs on a given subject.

- We had a Scientific Advisory Board and created a Scientific Review Council (SRC) which was a group of people that included scientists but also included parents or siblings of people with autism and clinicians - people with an extra hard core serious knowledge and involvement in the field.
  - This was important, because sometime you got a study that didn't make the cut off but was about something important, like a sleep study. For a group of disinterested people to say you can't fund this study because the N isn't right or the design isn't right it seemed inappropriate to us. So we put together a group of people who could look at a study and maybe rescue it.
  - This group functioned at the "scientific conscience" of CAN - they made big policy decisions and rescued certain things. The scientists who ended up being the most productive were often linked up to a senior person in the SRC who became their friend and provided support. That relationship was the critical thing in getting people to stick with us

- We would try to get projects that were as high risk as possible on one hand and then we took an extremely conservative approach and took a lot of money and put it into resource creation.
  - The most important thing anyone said to us was that we had to "become the data"; at that point we couldn't rely on people sharing data or raw materials. It was sort of an education to us that people didn't routinely share data.

- All we knew was that autism was genetic with 90% concordance in monozygotic twins, but to this day there are still no agreed upon biomarkers and diagnosis is still made by observation.
  - So people needed multiplex families with which to work. Columbia had some, and Duke had some, and Stanford had some, but no one had a critical mass.
  - We went to UCLA and said "We'd like to recruit for you from our database; if we bring these patients to you, all we want is that you make the DNA available to everybody." This was a radical idea and we didn't understand that. The scientists we spoke with said "We don’t do this. We need to work with the DNA as long as we can."

- As a result, we realized we couldn’t rely on making people share so we had to become the central resource and that's what we did and it's been the best return on investment.
  - We started the Autism Genetic Resource Exchange. Someone at NIH said there were only 700 multiplex families in the world - there are probably 700 in California.
  - We used the mothers to recruit.

- For example, in the normal process, you have a mother with two autistic kids. They all come to your center and wait for hours while you do tests. Then you have to try to get them to come back in to draw blood.
- We took the simple approach that the family affected with kids with autism is not the "subject" they are the customer and you can't do anything without pleasing them. You owe them - they don't owe you anything.
- We trained a whole army of diagnosticians and phlebotomists and sent them into the homes. We also put everyone on a list serve.

- We ended up with 100 multiplex families in the first year and now we have are over 500.
  - We took blood and immortalized it and made cell lines.
  - We ask people who use it to send back their genotypes and put it in database. In return for giving a couple of people early access to the DNA, we got back unpublished early data we posted on the web. For $7M, it enables $70 or $80M of research.
  - We do collections based on what people need, like cousins or half families. Four or five years into it we got NIMH to pay for part of it, but that will expire soon.
- The key thing is that anyone could get funding and materials. There was committee that reviewed applications, but anyone could get the grants. You could apply for grants and get biomaterials as part of it.
  - We tried to set up a different pricing structure for this but it didn't work because people complained and your mission is you want to get it into as many hands as possible.

- Pilot studies have been pretty successful where we kept up relations with people. Negative results are never a waste of money and we put that information on the web.

- Moving into contract research seems better. The field building stuff was important.
  - For example, no one knew how to do a clinical trial in autism, so we created a clinical trials task force.
  - No one know how to figure out if a kid was getting better because there was no sense of common measures for this so had a workshop on psychometrics.

- We were really sort of bootstrapping the field, but we have to guard against becoming institutional and what we hate the most. And that's the biggest danger CIRM has.
  - Are we becoming just incremental funders? We have to be innovative and aggressive. How do you do that? I don't know.

- I'm also concerned about California centrism; nothing good ever came to CAN without us giving things away. The more CAN gave things away and didn't worry about ownership or getting credit or getting cited, the better it was for us, not as an institution, but to the field. I have this deep feeling that the more you give it away the better it will be.
  - I know we have to fund in California but I hope we have banks of cell lines and assays available to everyone.
  - The biggest and best stem cell conference in the country should be put on by CIRM but the people invited to it and the people invited to CIRM workshops must not all be from California. Need to get a critical mass of people in other states.

- Encourage the creation of resources because maybe the bond won't be renewed. We want to have created something that can be reused so there is a return on investment for the 10 years of CIRM.

- CIRM also needs to periodically assess itself and look at itself and make sure it's still involving the stakeholders and being true to the mission.
  - As you still being urgent? Is there actually someone that can be helped?
  - We spent five years not funding treatment grants because we couldn't fine one to fund and that made us unpopular with some of our constituents but that's what was there.

Panel Discussion

Moderator: Zach Hall
Panel Participants: Michael Rudnicki, Michael Amos, Richard Insel, Ethan Singer, Jonathan Shestack

- **Q (Unidentified Audience Member):** One word that came up often was "management" or "proactive". There are many levels where this can occur and one is at the stage of review where you either take the NIH approach or issue a grant with provisos. Have any of you tried that second approach? How did it work? That is, have you ever said we'll give you the money but you must do the following? How might you structure it?
  - **A (Hall, CIRM):** Ethan, did I understand you don't pay people unless they do the work?
  - **A (Ethan Singer, HighQ):** For a typical one year project, recipients get half at the start and half at six months if their progress report comes in, or at eight months if it comes in at eight months. We don't take anything back but they won't get any more. It's in stages.
- **Q (Unidentified Audience Member):** If there is a research proposal that has interesting features but also problems, are you going back and in fact rewriting the investigator's proposal?
  - **A (Richard Insel, JDRF):** We don't do it with our regular grants or innovative grants, but in our new academic R&D program if someone sends in a good idea, or if we see something in the literature, we'll go after them.
    - We ask for 1 or 2 page description that starts a dialog and that goes back and forth in an iterative fashion. It's never final until its final and it goes back and forth until we get what we want.
    - We have rebuffed a lot of senior people and sometimes there are provisos.
    - We only do that for one aspect of our portfolio and so far we've enjoyed it and they have too and we're convinced it does make a better proposal. We craft the proposal and we manage it - we follow it much more closely.
  - **A (Mike Rudnicki, CSCN):** We will do that to shape proposals for particular projects of strategic interest. So we will shape them.

- **A (Signer):** We work with each and every one. Every project gets one staff person as the handler who stays with it all the way through. We are active partners in the process.
- **A (Michael Amos, NIST):** One thing to be aware of when you're trying to have a global competition is if you go back and work with organizations or individual companies especially and you help them more than it is perceived you helped someone else you may run into legal problems.
  - Our rule is: if it doesn't meet the criteria it doesn't meet the criteria and we offer debriefs to everyone who requests them. We don't go back and shape the proposals.
- **A (Rudnicki):** We go through a competitive process and it has to meet the cut but we may say "leave this out" or "emphasize this" in the letter of award and we manage that so it's achieved. The shaping primarily occurs in the letter of intent process and that's done for all applications.
- **A (Chiu, CIRM):** Flexibilty allows for rapid turnover and shaping of a product that achieves your mission but you delegate a lot of authority to staff. If, as a government agency, you're seen to help one project more than another some will say the paying field is not level.
- **A (Jeff Shestack, CAN):** What we do it its sort of an accelerated invitation to resubmit.
  - Someone wrote an interesting grant and it wasn't quite right, but people had an interest and made some suggestions and the investigator chooses to respond or not.
  - The SRC meets four times a year so they can get a quick response. I would think if you approach it like it won't seem like you're playing favorites.
- **A (Hall):** Where you are free to do that what you effectively do is hire good staff and empower them to go out and make these arrangements and make choices and actively work with people.
- **A (Shestack):** You also have it go back to a Scientific Review Council ultimately to protect your staff and the sprit of the organization.
- **A (Insel):** We shape our applications but they also go out for peer review and lay review.
  - Just one comment about fairness - ideally it's great to have reviews where all the grants are competing against each other. But for an organization like ourselves, the one group we have to be fair to be the patients and if we can accelerate research with these approaches, we have to.
- **A (Rudnicki):** This is true for all of us - it's shaped by peer review. It's not staff working independently.

- **Q (Don Reed, Patient Advocate):** It's so frustrating to see so many people separated. I think we need a national stem cell day or a stem cell stamp or something to unify people. How do we unify the different groups so we can fight more effectively?
  - **A (Insel):** There is a group called Faster Cures founded by Michael Milken that aims to bring disease specific foundations together to find common platforms and approaches for disease specific research.
  - **A (Rudnicki):** There is also a growing desire to build networks internationally.
    - CSN was responsible for forming a consortium of stem cell networks. The intent there is to work together on common problems especially when we get to clinic. The big problem is that will take a lot of resources to work together for clinical trials and get around jurisdiction problems.

- **Q (Mary Maxon, CIRM):** We're interviewing a lot of foundations and grant making agencies who make grants to for-profits to see what approaches work. Making for-profit grants and contracts is fraught with controversy but we're finding that grants or contracts in this area to certain foundations are more expensive (e.g., there's no tax deduction) so the organizations are careful to watch how those investments are made. So more and more of what I'm seeing is shared decision making where people are attending board meeting where the "two plus two" process is common. How do you feel about CIRM shaping a go / no-go decision at that level after a grant is made?
  - **A (Amos):** When we fund a proposal, a technical specialist well versed in the areas is assigned to the project to monitor it. We don't tell the companies what to do. We are allowed to work with them and make suggestions but they are not bound to do what we say. When we fund it's final.
    - Often companies reach out when they make progress or have problems and we work with them. We help them try to keep things going. Ours is a cooperative funding agreement so it's not exactly a grant or contract; they don't have to provide deliverables.
    - The goal is for us to facilitate and empower these companies to do new and exciting things, not to encumber and inhibit them. In shaping the projects, we're pretty selective in what we fund and we think we're pretty careful in what we do in the beginning. We work with the companies very closely to make sure they do what they need to do. Often they'll get to orals and we'll find holes and if they can address them we work with them on that basis. The funding decision is made based on the proposal.
    - But honestly, stuff happens - if you're <u>not</u> seeing changes during the project lifetime, you picked the wrong one. You will see this in high risk projects. Often things will change before the project even starts. You just have to be flexible, as long as what they do meet meets the criteria of innovation, risk, good R&D and meets the business criteria and they have to tell us what that is we'll let them change.

- **Q (Stephen Coles, UCLA; for Jonathan Sheestak):** I think the disease complex of autism is qualitatively different from a Huntington disease or diabetes diagnosis because it's a spectrum of disorders. I have seen in my experience the frustration of grass roots organizations in dealing with academia because we tend to be very arrogant. Let me mention another similar organization which is very suspect and the danger of a grassroots organization prematurely deciding they know how to cure the disease. It's unclear that all that effort and money that went into that [determining in mercury in vaccines was a cause of autism] was going to work.
  - **A (Sheetsak):** In the scheme of things no money went into that. Even if all we did was eliminate it from further discussion, it was money well spent.
    - What is true and does pertain to CIRM is how to bring many people together. We have complicated problems with different issues and it's a constant struggle to keep people in the tent.
    - We started with the assumption that we would never be able to close the flaps of the tent and say we've everything it. We're constantly trying to bring more and

more people into the tent. We know it's a dynamic process. You have to assume you will never get it right and you have to keep trying.
    - Funders like to take divisions in patient communities and balkanize them and use that as an excuse for doing nothing. Why don't we talk about problems we can all agree on and not worry about the controversial ones?

- **Q (Dave Rubinstein, City of Hope):** We've talked a lot about program management and governance. There's also a paradigm in science that the greatest creativity comes about with minimum of governance and management. How does that conflict resolve in your own minds, and what things and experiences have you had that have enhanced creativity? Not just efficiency, but that have caused scientists to come up with better ideas.
  - **A (Rudnicki):** Our job is not to do what the NIH or CIHR does. They have to keep funding what they're doing and do it better and better. All of our scientists are well funded by those sorts of basic science enterprises.
    - Our goal is to harness these people and begin to think in a translational way. To take their discoveries that might not be funded by standard mechanisms and try to translate them. We are a goal directed funding organization and we want to fund work in a way that identifies a path to the clinic. Often the NIH doesn't to that.
    - We also want to build multidisciplinary teams to bring this to fruition. We're very small and have to pick what we want to do because we can't do it all. Creativity for well funded scientists happens - they're creative people. We don't need to do a whole lot to foster that. They have lots of ideas
  - **A (Amos):** It depends on what research you're talking about. What the patient advocacy groups do is focus on their area and they bring in experts in a certain aspect. It's the right thing to direct some of the work because you're held accountable for the money that people have donated and you want people to keep donating.
    - When you talk about basic research, the less governance / management / oversight the better because you want people in basic research to be creative and go where they need to go to make those basic research discoveries.
    - When you're talking about technology development and specific deliverables or drugs, in the end if you know what the path should be and everyone agrees on it, when the guys you fund says what they will do, you have to watch them. Scientists tend to like to follow their noses, so it's hard to fund people who will manage a project to the end of a project and stay on task and do what they say and deliver things in the end.
    - Still, you want to stimulate free thinking, soon the basic science side you want to let people wander.
  - **A (Signer):** You ask an important question but part of the problem is "creativity" and "governance" can means lots of things.
    - I would slice it like this: Creativity is often about what you're going to do, and not how. I would argue that governance can be structured that it doesn't interfere with what you're going to do but helps with how you're going to do it.
    - This can be the case with stem cells. You can become the most knowledgeable collection of stem cell information on the planet. If someone has a great idea you are in the position to improve the execution of that idea by bringing to bear the knowledge and expertise that you have access to and that individual would not.

- This is, if you will, glorified peer review and we all know how valuable peer review is to science. It's all in the details - if you try to impose governance it won't work. If the governance is interactive and used to further the aims of both parties, it's often quite effective.

- **Q (Hall):** One of the things this has reminded me of is of the usefulness of workshops in formulating aims. We've done some of this as an ongoing way of asking, refining and sampling the best broad opinion in the field and using that as a way to generate ideas. This has underscored the importance of this in an ongoing way for our activities. Do any of you have experience with this
  - **A (Insel):** Beta cell regeneration was a new field for us, so we brought together a bunch of experts in our field and who work in other fields. You can foster creativity at this level with an interdisciplinary approach by brining people from different fields together and there's not enough of that.
  - **A (Signer):** You often reformulate the question that you thought had been formulated adequately. Sometime, you formulate the question and seek to answer it and you're stuck with the original formulation because only if new information comes in can you reformulate. Workshops are an excellent way to do that.

- **Q (Simpson):** The biggest challenge will be funding different levels in different ways. CIRM will want to put money into basic research and translational activities which carry the danger, if you have innovative research, of spending money with no payoff. It seems to me one of the biggest challenge is explaining to people that we put money into something and learned nothing except it didn't work. That's probably valuable in some context, but I'm not sure it gets accepted by the public. Can you offer advice to justify "dry holes" that will be inevitable?
  - **A (Hall):** Someone today said if you don't have lot of failures you not being adventurous enough. I have commented on the gap between the political and scientific cultures in California. People have to understand that not all science succeeds. If you are too successful you're not adventurous enough on setting those goals. That's a balance we'll have to strike.
    - It is an education matter in the end. It is also a policy matter and we'll discuss at a later session how to balance innovation and results and how to get the singles and not just the home runs to push things forward.
  - **A (Unidentified Audience Member):** Were seeing that in gene therapy trials. The field is in its infancy, but you can see there are negative results, but those are very informative as to what approaches won't succeed or what needs to be modified. So a negative or bad result on a translational line of research can be very informative
  - **A (Hall):** Another way to look at it is: it's just hard. As you progress through the narrowing down of the pipeline, all the things that looked good drop out. There's a squeeze on that and the private sector literature is full of examples of how you move from thousands of compounds to one in the clinic. Finding drugs is very hard and we have to see if cellular therapies will be different

- **Q (Patricia Olson, CIRM; on behalf of Jean Fontana):** Partnering with private industry will be part of what CIRM will have to do. How do we do that in transparent way because in some sense transparency is what we are really asked for?
  - **A (Amos):** One thing that's made ATP a success is companies can come to us with their coolest ideas and they're not afraid that someone who reviews the proposal will run off and copy it.
    - One thing that will cause a company to fail is to be too cagy and not telling us exactly what they are going to do. We can't make a decision unless we know what you're going to do.
    - So there has to be confidence in the process that companies would use in sharing their ideas with you. At the other end you have the public that wants to know what their money is going to.
    - The balance for ATP has been that the Board discussions, proposals, and funding decision are completely confidential to protect the individuals and the process that is used to do the work. The people who are asked to candidly share their opinions have to trust in the other board members and that what they say will never leave the room. Those discussions are confidential and that protects the process. In order to get people who are part of the selection process to feel comfortable making statements and being part of the process and giving their honest opinion you have to protect that.
- **Q (Chiu):** Once you fund something, is the application FOIA-able and how do you manage it?
  - **A (Amos):** No, it's exempted by an act of Congress. Anything a company sends us that is marked as confidential is exempt from FOIA forever.
- **Q (Olson):** What about transparency?
  - **A (Amos):** We openly discuss the process and share with anyone what the process is and how the proposals are selected. Companies can say whatever they want. If somebody calls me, I can't talk about it, but invite them to contact the company. We have a public abstract for people to access on our Website with a contact at the company and a contact at ATP for what we can talk about. Until the company releases any other information, it's their information and part of their IP.
  - **A (Rudnicki):** Our applications are confidential, but we do post the title of who's been awarded and how much in a non-disclosing lay abstract for public viewing.
  - **A (Amos):** People don't get upset over that because they see the quality of the stuff that comes out of the program. What really counts are results.
  - **A (Maxon):** My reading of Proposition 71 is that it says unpublished data and IP are exempt from public records act.

General Discussion

General Questions (Topic: People)

- **Q (Hall):** We will be facing a number of issues as we go forward for which there will be specific questions we need to answer to develop the strategic plan so we want to get your comments on some of these issues.
  - The first one is we need to support people. We heard about the emphasis JDRF puts on this and they spend 8-9% of their budget on training or investment in people. We have begun with a series of training grants and hope to have second round.
    - We also had some discussions to have grants that would train people for technical support positions, perhaps in partnership with the colleges and junior colleges in the state. We don't have more than vague ideas but several people have stressed the importance of that to us and we know there are several programs in the state to train biotech and biological technicians and it might be helpful to orient some of those to stem cell research.
  - The other question that comes up, and we saw this with JDRF, is the HHMI mechanism of supporting people rather than projects, of taking talented people and saying "What is your record of innovation and what have you done that's been interesting and what are your future plans?" with the real point being to try to identify outstanding people.
    - Two areas of interest for me are number one, young investigators for whom this might be very important, particularly in a field where the federal support has been restricted and number of people entering field had been less. So for someone starting out who wants to take a chance, one idea is to have a way to support them.
    - Many of you may not be aware that in medical schools, most clinical departments do not have hard money to support investigators. Junior faculty have to raise their own money, usually through a clinical practice plan, and have to spend so many hours per week in the clinic to pay for their salaries. The hardest thing about getting young clinical faculty involved is buying their time, that is, providing salaries to free them from clinical responsibilities not associated with research or education. I don't know if anyone has comments on any of these ideas of support people?
  - **Q (Reed):** It seems like there may be a problem with having enough staff do the mountain of chores that will descend on CIRM. Can some of these young investigators in the support field be trained to do some of the work?
  - **A (Hall):** What's in short supply is not talented people but the number of positions we have.
  - **Q (Reed):** The number of people doesn't seem sufficient for the mountain of stuff that's coming.
  - **A (Hall):** Out budget won't support more people; it's not that we can't find more people.
  - **Q (Reed):** Could we fund people with these young investigator grants to learn the technical support while they're doing the work that needs to be done?

- **A (Hall):** That's an interesting thought. That might pose some interesting challenges, and I suspect not, because Proposition 71 says only so much will be taken for administration and research administration, and those caps are pretty hard.
- **A (Gaye Crooks, CHLA):** As a clinical investigator myself, I was interested to hear your comments about young faculty trying to do clinical research. We're seeing, particularly in pediatrics, that it's more and more difficult to attract physician scientists into any field because of the overwhelming clinical crush and decreasing support medical schools and hospitals can provide for basic research.
    - There used to be fat in the system and there isn't now. We're seeing that as a problem in recruiting physician scientists so I think it would be a terrific thing if you could support that.

- **Q (Shestack):** The current system has a grant review group, it's a small group, mostly through people forced to convene from out of state, but hopefully you're talking about setting up many different grant programs - pilot and young investigator and ongoing training grants and facilities investment and innovator awards. Who's going to figure out how to review all that it systematically? As CIRM is set up now by legislation, it can't handle it. When you get down to disease specific grants, you really don't have the expertise or even the manpower.
    - **A (Hall):** If I could change one thing it would be the limit on the number of reviewers. It's going to pose an enormous problem.
        - It doesn't matter what kind of mechanisms we have built, it will be worse if we have many types of grants to review.
        - It's a huge problem that we're funding hundreds of millions with only 15 reviewers. I think JDRF said today that they have a budget of $100M and they have 150 outside reviewers.
- **Q (Shestack):** For CAN, the best experience came from outside, ad hoc reviewers who were invited in for a session and did have a tremendous lifetime burden. They brought a lot of enthusiasm to that moment and were then allowed to escape. Is it a strategic problem? Does it mean you have to fund fewer programs?
    - **A (Hall):** We need to make our scietific plan and then say we need more reviewers. I don't want the cart to drive the horse.
        - There's another wrinkle in that we can't triage because all grant decisions are made by the Board, so the Scientific Review Committee is only advisory. All decisions have to be made in a public meeting so the Board has to make the decision and the Committee can only make a recommendation in confidential session.
        - If the Committee triages and decides that a third of the grants don't merit full review, that's already making a decision and opens us up to litigation. All of us on the staff are acutely aware of this problem.

General Questions (Topic: Discovery)

- **Q (Hall):** With respect to investigator initiated curiosity driven grants' we've talked about using workshops to shape some of these. Someone asked whether we had a responsibility for

funding this basic science because the NIH won't. I think we can make the case that since NIH is not a source of funding for much of the basic science some of our efforts can be made in that direction. Should part of our portfolio include this?

- **A (Amos):** You have to have a blend. As years go on you have to make sure the pie is fluid because there will be things to emphasize in the beginning versus the end so you need a mechanism to reevaluate the portfolio.
- **A (Hall):** The real issue is the landscape is constantly changing. You're right, but we don't necessarily know what those changes may be. There may be possibilities we don't know about now that we will need to be open too.
- **A (Simpson):** It seems, particularly now with the lack of NIH money, that the portfolio does need to have a significant amount of investigator initiated activity but maybe later the NIH funding will come around. But it seems curiosity driven types of thing needs to be funded, though spokespeople for public may not always understand why you're doing it
- **A (Crooks):** It's essential in this very early stage of the field when the questions are of such a basic and technical nature that you have the investigator initiated questions driving it. The questions are so limitless and it's not well defined field.
  - The creativity we were discussing before comes from this type of grant and I would hope it would be a big part early on. The RFA way of doing things is a way of bringing in other fields and that's what will be the power of CIRM funding.

- **Q (Sheehy):** The fundamental question is how we divvy up this pie. To what degree are we replacing NIH funding and to what degree are we creating an infrastructure to support stem cell research - the people, a stem cell bank, and shared resources? What should our role be in doing that? In the early days maybe the shared platform and key discoveries is what people will run with.
- **Q (Shestack):** In early days there will probably be a lot of basic, technical research that everyone can benefit from. What is the mechanism at CIRM for designing the priorities and the ratios of the portfolio? How is it actually going to be done?
  - **A (Hall):** That's what we're trying to do in this process. Were trying to think about these questions. We will have lots of different interests. What we come out with will be a medley of those interests. We're hoping we get the best ideas. No one will be completely happy with what we come up with it. We're not talking numbers at this stage but what we want to include.
- **Q (Shestack):** There will be a document that will lay out a mixed portfolio, but how do we track progress?
  - **A (Hall):** We need to build in a mechanism to say in three years are we on track. The trick will be to build it in. Bob Klien makes a point about the necessity and importance of having stability in our support over ten years but we have to be careful about saying to investigators that we will offer <u>you</u> support for ten years. We have to design it in a way that we don't get frozen in. It will be a challenge in grants management to figure out how to do this every year so we'll have extra money each year. We will need to have some way to make sure it is continually being renewed.

- **Q (Steve Peckman, UCLA):** The CIRM Scientific Meeting in the fall went a long way toward developing the CIRM's goals. The science needs to drive the process. Where the

science is now and where its going will determine how the money should be divvied up and into what areas because we'll learn as we go.

- **A (Hall):** That was a terrific first step in our scientific strategic planning process. An account of the meeting is now available on the web and includes a list of recommendations.

- **Q (Duane Roth, Alliance Pharmaceutical Corporation):** I'd like to thank the panels for sharing your diversity of experiences. The most important thing we can do is set a framework for how we'll go about approaching the funding of all these mechanisms we're talking about. If we get the framework right we can fill in the details later.
  - I heard the word "comprehensive approach" - the discovery / development / delivery process will be important and we need to get the balance right and it will change over time.
  - I also heard the word "de-risking", using funds to de-risk things so they can be funded by the private sector.
  - We also need to "mind the gaps" as someone said earlier. That's where we need to come in - where there are gaps and the system isn't working and things aren't moving ahead.
  - The last one was to leverage financing and we need to think about that and make sure whatever we do with the IP policy doesn't prevent that leveraging from happening.

- **Q (Hall):** Let's talk for a moment about project driven research. Mike Rudnicki described starting out in disease specific areas and then moving horizontally to have enabling technology that would benefit a variety of fields. My own view is we will need, in addition to horizontal things, some vertically oriented projects. There is a choice in this.
  - We could pick out disease and put funds in those areas but that's a complicated issue and sets up issues of why we chose one disease area over another.
  - Another possibility would be to ask our researchers we're interested in picking a number of diseases and then funding vertically organized projects that would go from basic science, through the preclinical and clinical research and development stages, and finally into the clinic and say to people it's up to you to get the best talent in the state for each of the phases.
    - We would need to come up with a plan that doesn't call for supporting everyone on the project for a long period but phasing it in and out based on your stage of development. Put a project together using the best people in the state (and out of state if they will pay for it), tell us what milestones you will use, and tell us how you'll manage the project. Put together something that will move from one phase to the other for a disease or group of diseases and we would pick the ones most likely to succeed or is best organized.
  - **A (Amos):** Have you taken a survey to see where in the research continuum people are who might be applying to the CIRM?
    - If there's a lot of basic research that needs to get done, you have to do that, but if there's interest across the spectrum, you need to consider that too. Ten years is not a lot of time and you have to figure out where the state art is and go from there and build your portfolio
- **Q (Hall):** We're going to place multiple bets. We won't say we only need basic research. This may be premature, and we will have to offer long term support to say you need to figure out how to get stem cells to differentiate into the proper kind of progenitor cells, how and

where to put them, how to de-risk it, we'll need an animal model to validate that, there may be hope we can move into clinical trials. We can offer, in the state of in partnership, all parts of that.

- **A (Amos):** Traditionally, the focus has been on one protein or gene, but I think it's incumbent to start thinking in terms of the new philosophies more on the system biology side and actually looking at a cell as whole system and not as just one protein. Cells don't work one protein at a time. The technologies that would be needed to understand those things for all of stem cell research could be of great value.
- **A (Signer):** I'm not sure what I'm about to suggest is appropriate, but you set up the implicit opposition of people versus projects. Maybe neither is right and the way to think about it is to support questions.
  - Suppose you had an ad hoc advisory group of people outside California to define the interesting questions of the moment and the resulting RFA will be about whom would like to answer this question and how would you do it.

- **Q (Hall):** We have a number of questions like that that came out of our conference that are very clear. We will have RFAs on some of these very specifically. Given the state of stem cell science, we will have the luxury of supporting multiple things at the beginning. I don't see us doing all of one thing. I like Richard Insel's menu and if they can do that with $100M, we can do it with $300M. The question is to think about the possibilities of the things we want to do. It may be it will be useful to have an ongoing external advisory group that evaluates our portfolio from time to time.
  - **A (Rudnicki):** I would urge you not to do the same old thing. You have a chance to innovate and be creative to create structures and programs that meet your strategic needs and the needs of California to pursue particular scientific problems so don't be confined by how other organizations have done things. Be creative and innovate. Do not be conventional or you will be to some extent fostering mediocrity.
  - **A (Amos):** You need to have the balance between big science and small science.

- **Q (Oswald Steward, Ph.D., UC Irvine):** Do any of you have or know of any funding agency that has experience with the opposite, investigator driven submissions not for a proposal but for a structure? In other words, asking scientists to tell us what the optimal way is to go about this process?
  - **A (Amos):** Agencies like Homeland Security do that and have open forums and they get unsolicited proposals all the time. We don't.

- **Q (Shestack):** I want to talk about the disease specific issues. You have to balance scietific opportunity with the political reality of CIRM's funding. It goes back to leverage - it may be that $5M of CIRM money in ALS research becomes significant amount of money in the total ALS budget in the country. You have to think about the opportunities you have to jump start the fields that will come back and build your field.
  - CIRM has to be willing to deal with potential political fall out by picking diseases and writing RFAs and saying we are interested in applications for specific diseases and driving people in those fields. You could drive people in autism to be working on neuronal stem cells and can make a huge difference that will pay off five years down the road.
  - We should consider actual partnerships with some of these groups that have scientific advisory groups and funding mechanisms and joint funding to take some of the political

sting out of it. We assume everyone will get their noses out of joint I think everyone will be happy to step aside as long as someone is getting to step up.

- You have to remind yourself you're here to cure specific diseases
  - **A (Rudnikci):** I wasn't saying we shouldn't fund disease specific research. My concern is setting up silos. Good projects can come from different areas and be driven by partnerships and that absolutely fine.
  - **A (Hall):** The hard thing is how you make that choice and who makes it. My personal view if the best ideas come up from the bottom. You can give incentives to people to make the case for a disease or group of diseases; we could even come up with planning money. Rather than choose the disease, let them make the case to us and we go ahead and fund it. Rather than make an *a priori* judgment about which disease is ready, have people make the case for it.
  - **A (Shestack):** If you do that, the answers will be predictable. You have to do a little social engineering and rescue people who don't have that establishment to being with in these diseases.
  - **A (Hall):** My thought would be not to have this competition so you end up with the same winners, but so that you uncover things you never thought of.

- **Q (Reed):** Everyone wants to make sure nothing promising gets locked out. What if we thought about what are the commonalities among diseases? For example, diabetes, autism, spinal cord injury and MS all have demyelination of nerves as a common feature. Could we encourage people to look at the common things that may bring them together?
  - **A (Amos):** You're at a point where you can change the world. You have a unique opportunity to recreate something and you're not limited so you have to look at what has and hasn't worked. Sometimes one gene or one protein or one disease at a time doesn't take you where you need to go. Is it better to do the same thing that been tried and hasn't succeeded on a bunch of different diseases or is it better to create something that will completely change the way disease and disease mechanisms and determined and defined and discovered?